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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/679,987	10/07/2003	Bruce A. Malcolm	JB01587	4551

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SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
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KENILWORTH, NJ 07033-0530

EXAMINER

STRZELECKA, TERESA E

ART UNIT	PAPER NUMBER
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1637

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/679,987

Applicant(s)

MALCOLM ET AL.

Examiner

Teresa E. Strzelecka

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 January 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3, 7-14 and 18-22 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 7-14 and 18-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>1/11/07</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This office action is in response to an amendment filed January 11, 2007. Claims 1-22 were previously pending, with claims 4-6 and 15-17 withdrawn from further consideration. Applicants cancelled claims 4-6 and 15-17 and amended claims 1, 2, 12 and 13. Claims 1-3, 4-14 and 18-22 are pending and will be examined.

2. Applicants' amendments overcame the rejection of claims 1, 9-12 and 20-22 under 35 U.S.C. 102(b) as anticipated by Karamohamed et al. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" section below.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on January 11, 2007 was filed after the mailing date of the non-final office action on July 11, 2006. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

4. Applicant's arguments filed January 11, 2007 have been fully considered but they are not persuasive. Only the arguments regarding the rejection of claims 2, 3, 7, 8, 1, 14, 18 and 19 under 35 U.S.C. 103(a) over Karamohamed et al. and Lohman et al. will be considered, as they are pertinent to the rejections presented in this office action.

Regarding this rejection, Applicants argue that one of skill in the art would not be able to predict whether the combination of teachings of Karamohamed et al. and Lohman et al. would result in a sensitive and continuous RdRp assay using ATP detection by luciferase, since instead of dATP used in a ATP would need to be used in the RdRp assay, and ATP is more active than dATP as a luciferase substrate. Applicants further argue that it would not be possible to predict whether the

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modifications made to dATP would be effective with ATP, and it was not known whether an ATP analog could serve as a substrate for RdRp in the polymerase reaction without interfering with the luciferase assay.

First, Applicants argue limitations which are not present in the claims, namely, continuous and sensitive RdRp assay. If the assay does not involve the presence of luciferase detection simultaneous with the polymerization reaction, one of skill in the art would know how to decrease background caused by the presence of unused ATP in the polymerization reaction before measurement of the signal produced by luciferase. Then the issue is moot if only poly(G) or poly(C) polynucleotides are used as templates. As to the issue of ATP α S being a substrate for an RNA polymerase, as evidenced by Griffiths et al. (Nucl. Acids Res., vol. 15, pp. 4145-4162, 1987), RNA polymerase uses ATP α S as a substrate with the same efficiency as ATP (Abstract; page 4146, last two paragraphs; page 4147; page 4148, first paragraph; page 4149-4151; Fig. 2). Therefore, the only remaining issue is whether it would have been obvious to one of skill in the art to use ATP α S in the luciferase assay. As evidenced by Sillero et al. (Pharmacology and Therapeutics, vol. 87, pp. 91-102, 2000), who investigated various nucleotides in a reaction catalyzed by firefly luciferase (page 92, last paragraph; page 93). Sillero et al. point out that the production of light requires formation of a complex between the enzyme, luciferin and AMP (equation 7) and conclude in the last paragraph of page 93 and first paragraph of page 94:

“These results indicate that adenine nucleotides with at least a triphosphate chain and with an intact α -phosphate are the preferred substrates for the formation of the E•LH2-NMP complex. Nucleotides best accepting AMP from E•LH2-AMP are those that contain at least a triphosphate chain and an intact terminal PPi moiety.”

Therefore, it would have been obvious to one of skill in the art that substituting ATP α S for ATP would not inhibit the polymerization reaction and that ATP α S would not serve as an efficient substrate for luciferase.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. Claims 1-3, 7-14 and 18-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Karamohamed et al. (Biotechniques, vol. 24, pp. 302-306, 1999; cited in the previous office action) and Lohmann et al. (J. Viral Hepatitis, vol. 7, pp. 167-174, 2000; cited in the IDS and in the previous office action).

A) Claims 1 and 12 will be considered together in claim 12, which is a species of claim 1.

Regarding claims 1 and 12, Karamohamed et al. teach a method of detecting RNA polymerase activity, the method comprising:

(a) providing a primer oligonucleotide having a 3' OH (page 302, last paragraph; page 303, first paragraph; page 304, second paragraph);

(b) contacting said primer oligonucleotide with a template polynucleotide and allowing hybridization to occur to form a hybridized polynucleotide (page 302, last paragraph; page 303, first and second paragraph; page 304, second paragraph);

(c) adding an RNA-dependent polymerase to said hybridized polynucleotide to produce a mixture (page 303, first and second paragraph; page 304, second paragraph);

(d) adding a PPi detection mixture to said mixture (page 303, second paragraph; page 304,

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second paragraph);

(e) adding a substrate mixture comprising a nucleotide triphosphate or an analog thereof to said mixture (page 303, second paragraph);

(f) adding a compound that is or is suspected of being an inhibitor of said RNA-dependent polymerase (page 303, third paragraph; page 304, fifth paragraph; Table 2); and

(g) measuring a product of the PPi detection mixture (page 303, last paragraph; page 304, first and second paragraphs, Fig. 1-3);

wherein apyrase is not part of the mixture (Table 1; page 303, second paragraph), and steps (c), (d), (e) and (f) may be performed simultaneously or separately in any order.

Regarding claims 9 and 20, Karamohamed et al. teach detection mixture comprising luciferase, luciferin, ATP sulphurylase and AP, with the product being emitted light (page 303, second paragraph; Table 1).

Regarding claims 10 and 21, Karamohamed et al. teach measuring light with a luminometer (page 303, second paragraph).

Regarding claims 11 and 22, Karamohamed et al. teach a luciferase operating at 23° C (page 303, last paragraph). Since Applicants did not define the term “thermostable”, the luciferase of Karamohamed et al. is inherently thermostable up to 30° C (page 304, fourth paragraph). Further, Karamohamed et al. teach luciferase stable at higher temperatures (page 306, first paragraph).

B) Karamohamed et al. teach detection of reverse transcriptase activity, but do not teach RNA-dependent RNA polymerase from Hepatitis C virus or specific primers and templates.

B) Regarding claims 1-3 and 12-14, Lohmann et al. teach evaluation of Hepatitis C virus NS5B activity in the presence and absence of inhibitors (Abstract; page 169, last paragraph; Fig. 2; page 170, first and last paragraphs; page 171, paragraphs 1-3; Fig. 3).

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Regarding claims 7 and 18, Lohmann et al. teach synthetic poly(G) and poly (C) (page 171, last paragraph).

Regarding claims 8 and 19, Lohmann et al. teach the primer and template polynucleotide being the same molecule (page 169, last paragraph; Fig. 2).

It would have been *prima facie* obvious to one of ordinary skill in the art to have tested the RNA polymerase of Lohmann et al. using the method of Karamohamed et al. The motivation to do so, provided by Lohmann et al., would have been, as stated by Lohmann et al. (page 167, first two paragraphs):

“The hepatitis C virus (HCV) is a major causative agent of sporadic and transfusion-associated liver disease worldwide [reviewed in 1,2]. The majority (80±90%) of all infections become persistent and lead to various clinical outcomes ranging from an inapparent carrier state with almost normal liver function to chronic active hepatitis. Overall, ~ 50% of all infections lead to chronic hepatitis with 20% of those developing liver cirrhosis. Furthermore, patients with chronic hepatitis C, in particular those with cirrhosis, are at high risk of developing hepatocellular carcinoma, and HCV is the second most common aetiological agent in the development of this disease. Chronic hepatitis C, to date, can only be treated with interferon- α (IFN- α). However, non-responders and relapsers are frequent, and sustained biochemical response is achieved in only ~20% of patients [reviewed in 3]. Although this number can be increased by combination therapy with the nucleoside analogue ribavirin, recent data indicate that even in this case at best 40% of treated patients show a sustained response and the number falls to 16% in IFN- α nonresponders [3]. Therefore, a more effective antiviral therapy is urgently required.”

The motivation to do so, provided by Karamohamed et al., would have been as stated by Karamohamed et al. (page 306, last paragraph):

“In conclusion, we present a real-time assay for continuous detection of RT activity. The assay is simple, sensitive and non-electrophoretic, and there is no need for labeled nucleotides. The applications of the assay are very broad, which opens up new possibilities for obtaining a detailed picture of the events involved in RT reactions, such as the effects of different compounds on RT activity.”

7. No claims are allowed.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

Teresa Strzelecka
4/3/07